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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,053	04/12/2005	Tomohisa Hattori	1254-0260PUS1	6321

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EXAMINER	
ROBINSON, BINTA M	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
10/11/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/510,053	HATTORI ET AL.	
	Examiner	Art Unit	
	Binta M. Robinson	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 6-14 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 6-14 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 12/22/04;10/01/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Hasegawa et. al. Hasegawa et. al. discloses the instant method for inhibiting a phosphodiesterase IV with the instant compounds, 72, 73, 76, 84, 135, 136, 140, 141, 142, 143, 144, 153, 154, 155, 162, 163, 165. At pages 46-89, see the instant compounds.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hasegawa. (See Reference N). Hasegawa et. al. teaches the instant method of inhibiting phosphodiesterase IV with the compound as shown in Formula I, wherein Ar1 is (substituted) pyridyl; Ar2 is (substituted) phenyl; R1 is H, alkyl; R2 is H, alkyl, cyano or alkoxycarbonyl; R3 is H or (substituted) alkyl; X is O or S; A and B are each H, OH, alkoxy or alkylthio, or alternatively they together form oxo, thioxo, =N-Y (wherein Y is

dialkylamino, OH, aralkyloxy or alkoxy) or Z1-M-Z2 (wherein Z1 and Z2 are each O, S or optionally alkyl-substituted imino; and M is alkylene or phenylene) or B may be 1-alkylimidazol-2-yl with A being OH; and n is an integer of 1 to 3. At page 1, see the abstract. The difference between the prior art method and the instantly claimed methods is the teaching of the use of a generic compound which overlaps in subject matter with the instant genus of compounds. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds and to use these compounds to inhibit phosphodiesterase IV. Accordingly, the instant methods are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 6-14 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 14-16 of U.S. Patent No. 6313153. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent claims a subgenus of the instant genus of compounds and the instant method of use.

'153 teaches the instant compound as shown in Formula (I') which wherein the genus claimed is the same as the instant genus with the exception of the proviso that is claimed in lines 1-7, at column 83 and the instant method of use. See claim 4. The difference between the prior art compound and method and the instantly claimed compounds and method is the teaching a subgenus versus a genus of instant compounds. The '153 genus claims a proviso, unlike the instant claims. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds. Accordingly, the compounds and methods are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 10 recites the limitation "Ar^2 is further substituted with at least one member selected from the group consisting of a halogen atom, a hydroxyl group, an optionally substituted amino group, a substituted C1-6 alkoxy group, an optionally substituted C1-6 alkyl group, an aryl group, a C1-6 alkylthio group, a carboxyl group, a C_{1-6} alkoxy-carbonyl group, a sulfamoyl group and a group –O-CO-R^4 (where R^4 represents a C_{1-6} alkyl group, an aryl group, a C_{1-6} alkoxy group, or an optionally substituted amino group" in lines 3-7. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating chronic bronchitis, hives, allergic rhinitis, conjunctivitis, gonarthrosis, septicemia, ulcerative colitis, manic-depressive psychosis, schizophrenia and Chrohn's disease, does not reasonably provide enablement for treating bronchial asthma, rheumatoid arthritis, atopic dermatitis, or all phosphodiesterase IV-involving diseases or preventing any of the diseases claimed. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The

factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The main issues are the correlation between clinical efficacy for treatment of the various diseases claimed and Applicants' *phosphodiesterase IV inhibitory* assay.

a) Determining if any particular claimed compound would treat any particular disease claimed would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different diseases claimed, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large quantity of experimentation. b) The direction concerning treating these diseases is found in pages 16-46, which merely states Applicants' intention to do so. Applicants describe formulations at page 14. Doses required to practice their invention are described at line 11, page 14. A 20-fold range of doses is recommended. Since no one has ever used phosphodiesterase IV inhibitors to prevent any of these

diseases or at the time of the invention to treat atopic dermatitis or rheumatoid arthritis, how is the skilled physician to know what dose to use for each of these different diseases? There are no guidelines for determining the doses needed to provide an inhibitory effect on the phosphodiesterase IV inhibitors. Are the identical doses to be used for treating these unrelated diseases? c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of the diseases claimed with these compounds which are phosphodiesterase IV inhibitors which involves physiological activity. e) The state of the clinical arts is that there were no disease modifying treatments for rheumatoid arthritis in 1999, and that it is not the state of the art to prevent any of these claimed diseases. See column 1, page 1315 of Dyke et. al. PDE 4 inhibitory activity has been shown to be bronchodilatory and to reduce airway responsiveness in Asthma. However, CDP 840 and the allergen-induced asthmatic response was evaluated after twice-daily oral administration and there was no effect on the early asthmatic response and only a marginal effect was seen on the later one. See column 2, page 469 of Doherty. There is no in vivo pharmacological data correlating PDE 4 subtype selectivity with a therapeutic benefit or adverse effect liability. See page 784 of Odingo. For these inhibitors, the consequences of their action in vivo should become apparent in the future and

will determine whether this is a viable strategy to address the dose-limiting effects that have been a problem for PDE 4 programmes for years. See page 784 of Odingo. Clinical evaluation of PDE4 inhibitors has mainly been carried out for asthma and (chronic obstructive pulmonary disease) COPD. Results in asthma studies have been disappointing. See page 784 of Odingo.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was

sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). h) The scope of the claims involves all of the thousands of compounds of formula I in claim 1 as well as the myriad of diseases claimed in claim 1. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Janet Andres can be reached on 571-272-0867.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)-272-1600.

BMR
October 1, 2007

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER